MEAN PLATELET VOLUME IN ACUTE MYOCARDIAL INFARCTION

Dissertation submitted for

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CERTIFICATE

This is to certify that this dissertation titled **"MEAN PLATELET VOLUME IN ACUTE MYOCARDIAL INFARCTION"** submitted by Dr.ANOOP K.KOSHY to the faculty of General Medicine, The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I, Dr.ANOOP K.KOSHY, solemnly declare that the dissertation titled **“MEAN PLATELET VOULME IN ACUTE MYOCARDIAL INFARCTION”** has been prepared by me.

This is submitted to the Tamil Nadu Dr.M.G.R.Medical Universiy, Chennai, in partial fulfillment of the regulations for the award of M.D.degree Branch I (General Medicine).

Place : Madurai

Date : DR.ANOOP K.KOSHY

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Above all I thank the Lord Almighty for his kindness and benevolence.

CONTENTS

INTRODUCTION

INTRODUCTION

Cardiovascular disease is an epidemic of modern society. Myocardial Infarction is a major cause of morbidity and mortality in the world. Despite the impressive strides in diagnosis and management over the past three decades, acute myocardial infarction continues to be a major public health problem in industrialized world and is becoming an increasingly important problem in developing countries. Because acute myocardial infarction may strike an individual during the most productive years, it can have profoundly deleterious psychosocial and economic ramifications.

After rupture of an atherosclerotic plaque in a coronary artery, there is platelet adhesion, activation and aggregation leading to the formation of a thrombus and ultimately culminating in acute myocardial infarction. So the more reactive the platelets are, the higher the chances for myocardial infarction.

Bancroft et al (2000) stated that platelet volume is a marker and possibly a determinant of platelet function in that, larger platelets are more reactive than normal sized platelets.

Martin et al (1983) found an association between increased mean platelet volume and increased occurrence of myocardial infarction. But studies conducted by Halbmayer et al (1995) observed no such association.

Thus the role of platelet volume as a risk factor for the occurrence of myocardial infarction remains unresolved and further studies are definitely needed. Hence the hypothesis considered for the present study is “Platelet volume is not associated with myocardial infarction”. However, the proposed study will also help to confirm or refute the published reports on platelet volume in myocardial infarction.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The role of platelets in acute myocardial infarction has been appreciated for several decades. Yet the last 5-10 years have seen a dramatic increase in the understanding, development, clinical evaluation and therapeutic application of platelet inhibitor therapy.

Platelets play an essential role in haemostasis, thrombosis and coagulation of blood. These tiny cells previously described as “sponges” (Adelson et al, 1961) are known to engage in a complex repertoire of biochemical and molecular activities designed to prevent haemorrhage.

PLATELET STRUCTURAL AND FUNCTIONAL ANATOMY

Light Microscopy

On Wright-Glemsa stained blood smears, platelets appear as small anucleate, ovoid or round cells, with a pale grayish blue cytoplasm that contains homogeneously distributed purple-red granules.

Dimensions

The volumes of circulating platelets from a single individual are heterogeneous and exhibit a lognormal size distribution; and the platelet volume in a single individual (mean platelet volume, MPV) varies from 7 to 9

femtolitres. (Paulus, 1975; Martin et al, 1982; Stenberg and Levin, 1989; Corash, 1977).

Electron Microscopy and Subcellular Organelles

By scanning electron microscopy, circulating blood platelets appear as flat discs, with smooth contours and rare spiny filopodia. Scanning electron microscopy also reveals random openings of a channel system, the surface connected canalicular system, which invaginates throughout the platelet and is the conduit by which granule contents exocytose after stimulation. Although the platelet is anucleate, transmission electron microscopy reveals a cytoplasm packed with a number of different organelles essential to the maintenance of normal haemostasis.

Glycocalyx

Structure : A glycocalyx, 15 to 20 nm thick, is visualized by transmission electron microscopy and contains glycoproteins, glycolipids, mucopolysaccharides, and adsorbed plasma proteins.

Function : The glycocalyx has a net negative surface charge due to sialic acid residues on the proteins and lipids; the charge is thought to minimize attachment of circulating platelets to each other (Coller, 1984). This structure is rich in carbohydrate moieties of membrane-associated glycoproteins, which serve as receptors to mediate transfer of signals by stimulatory agents. The

glycocalyx interacts with platelet activators to facilitate platelet adhesion and aggregation.

Plasma Membrane

Structure : The platelet plasma membrane is a typical trilaminar membrane with glycoproteins, glycolipids, and cholesterol embedded in a phospholipid bilayer.

Function : The plasma membrane contains sodium and calcium ATPase pumps, which are important for maintaining ionic homeostasis. It has a specialized role in providing a surface for the acceleration of blood coagulation, in that a specific platelet coagulant protein, platelet factor 3, resides in this lipoprotein-rich unit membrane.

Surface-connected Canalicular System

Structure : The surface-connected canalicular system, also called the open canalicular system, weaves throughout the cell cytoplasm in a tortuous fashion.

Function : The functions of the surface connected canalicular system are to provide a route of entry and egress for molecules, an internal reservoir of membrane to facilitate platelet spreading and filopodia formation after adhesion and a storage reservoir for membrane glycoproteins that increase on the platelet surface after activation.

Dense Tubular system

Structure : Unlike the surface-connected canalicular system, the dense tubular system is a closed-channel system consisting of narrow, membrane limited tubules, approximately 400 to 600 A in diameter. It is, infact, residual smooth endoplasmic reticulum from the megakaryocyte.

Function : This channel system is involved in the regulation of intracellular calcium transport because it has been reported to selectively bind, sequester, and release divalent cations after activation. The dense tubular system is also the site of prostaglandin synthesis in platelets.

Cytoskeleton

General Structure : The platelet cytoskeleton contains 30 to 50% of total platelet protein and is made up of three major structural components : an actin microfilament network present throughout the cytoplasm, a micro tubule coil localized at the platelet periphery and a membrane skeleton comprising a network of short actin filaments that underlies the inner surface of the plasma membrane. Although they are distinct structures, interconnections between these elements are present.

Structure and Function of Specific Cytoskeletal Elements

Actin Microfilaments : Twenty to thirty percent of total platelet protein is made up of actin (Pollard, 1990). Actin exists in two forms, G-actin (actin monomers) and F-actin (polymerized actin). In the unstimulated platelet, 30 to

40% of actin is polymerized into filaments; the balance of actin monomers are prevented from polymerizing by proteins such as profilin or thymosin B4 that sequester monomeric actin, or by proteins that cap filaments in the intact cell, such as gelsolin.

Upon platelet activation, the proportion of filamentous actin rapidly increases to 60-70%. Actin monomers polymerize onto filaments at platelet peripheries and bundles of new filaments form to fill developing filopodia.

Microtubules : A circumferential microtubule band that supports the discoid form of the platelet is made up of two nonidentical subunit proteins (alpha and Beta tubulin) associated with microtubule associated proteins (MAPs). The 25 nm diameter microtubule coil lies adjacent to, but does not touch, the plasma membrane.

Microtubules are present primarily in their polymerized form in unstimulated platelets. Platelet activation results in microtubule disassembly, then reassembly; such alterations in the marginal microtubule bundle result in platelet shape changes.

Membrane Skeleton : The short actin filaments of the membrane skeleton, which underlie the inner surface of the plasma membrane, together with the microtubule coil, are thought to help stabilize the platelet discoid shape.

Two major platelet membrane glycoproteins, GP IIb-IIIa and GP Ib-IX are associated with the membrane skeleton.

Granules

Platelets contain four distinct populations of granules: alpha granules, dense bodies, lysosomes, and microperoxisomes. After platelet stimulation by agonists, granules fuse with channels of the surface-connected canalicular system and extrude their contents (White, 1974). Internal contraction is required for this extrusion and ultimate discharge into the surrounding medium.

α - Granules :

Structure : α Granules are the predominant granule type in the platelet. The α granule has been subdivided morphologically into three distinct zones by electron microscopy : an electron- dense nucleoid that occupies the bulk of the granule, a peripheral zone of lower electron density that lies adjacent to the granule membrane and 1 to 6 tubular structures that reside in the electron lucent peripheral zone.

Content : B-thromboglobulin and platelet factor 4 have been localized to the dense nucleoid. Von Willebrand factor is present in the tubular structures of the granule peripheral zone. Thrombospondin, and fibrinogen are present in the granular matrix. Other proteins present in α granules include albumin, immunoglobin G (IgG), fibronectin, platelet derived growth factor, GPIIb-IIIa, Beta amyloid protein precursor, factor V, multimerin, a factor V/Va binding

protein, transforming growth factor β1 and a plasminogen activator similar to tissue plasminogen activator.

Proteins present on the α – granule membrane include P-selectin, GP IIb / IIIa, granule membrane protein – 33 (GMP-33), CD9, platelet – endothelial cell adhesion molecule 1 (PECAM-1) and osteonectin.

Dense Bodies :

Structure : Ultrastructurally, dense granules have a bull's eye appearance. They are the most electron-dense organelles in platelets.

Content : The principal constituents of dense granules are a nonmetabolic pool of adenine nucleotides (adenosine triphosphate and diphosphate, ATP and ADP), PPi, calcium and magnesium and serotonin (5-hydroytryptamine). In addition, dense bodies contain guanosine triphosphate and diphosphate (GTP and GDP). The dense granule membrane contains P – selectin and granulophysin.

Lysosomes :

Structure : Lysosomes are small vesicles of approximately 175 to 200 nm.

Content : Lysosomes are the only platelet granules that contain acid hydrolases. Platelet lysosomes contain a large variety of enzymes, including β hexosaminidase and β glycerophosphatase. Lysosomal membrane glycoprotein

(LIMP-CD63) and lysosomal associated membrane proteins 1 and 2 (LAMP-1 and LAMP-2) become expressed on the plasma membrane after activation.

Microperoxisomes :

Structure : Microperoxisomes are small (90-nm) granules that are relatively few in number in platelets and can be demonstrated only cytochemically.

Content : They are reactive with alkaline diaminobenzidine medium. The enzyme responsible for the cytochemical peroxidase activity in microperoxisomes is catalase.

Coated Vesicles :

Structure : Coated vesicles are 70 to 90 nm organelles

Content : The polyhedral coat on the surface of these vesicles is composed of clathrin. Coated pits and vesicles transfer plasma components to platelet granules (Behnke, 1989).

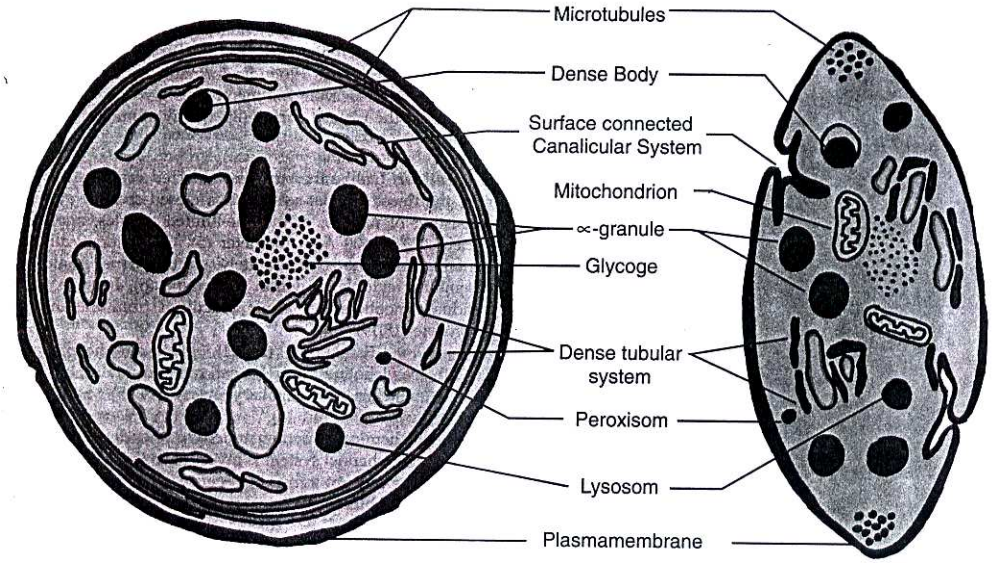
Mitochondria :

Structure : Mitochondria in platelets are similar, with the exception of smaller size to those in other cell types. There are approximately seven per human platelet.

Content : Mitochondria are the site of activity for all components of the respiratory chain and for almost all enzymes in the citric acid cycle.

Glycogen

Platelets contain small particles of glycogen or masses of closely associated glycogen particles; these play an essential role in platelet metabolism.



(Diagram of a human platelet displaying components visible by electron microscopy and cytochemistry)

PLATELET PHYSIOLOGY

Platelet Lipids and Proteins

Membrane Lipids

Phospholipids constitute 80% of the total platelet lipid, although smaller amounts of neutral lipids and glycolipids are also present. The five major phospholipids identified in human platelets are phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, phosphatidylserine and phosphatidylinositol. Almost all platelet fatty acids are esterified in phospholipids, leaving only trace amounts of free fatty acids. Arachidonic acid, the precursor of prostaglandins and thromboxanes, is enriched in these phospholipids and the metabolism of arachidonic acid is critical for normal platelet function (Marcus, 1976).

Neutral lipids make up approximately 28% of total platelet lipids, the predominant neutral lipid being cholesterol.

Membrane Glycoproteins :

Platelet membrane glycoproteins mediate a wide number of adhesive cellular interactions. These glycoproteins function as receptors that can receive signals from outside the platelet, facilitating cell – cell interactions; binding of specific ligands to these receptors results in distinct platelet responses to the external environment.

Glycoprotein IIb / IIIa : Glycoprotein IIb-IIIa is the principal receptor on the platelet plasma membrane (Philips et al, 1988). It is a member of the integrin family of proteins. A Ca2+ dependent conformational change in GP IIb-IIIa after platelet agonist indued stimulation facilitates strong binding to fibrinogen and VWF resulting in cross linking of GP IIb-IIIa molecules on adjacent platelets and platelet aggregation.

Glycoprotein Ib-IX : Glycoprotein Ib mediates the interaction of platelets with VWF. GP Ib also functions as a binding site for thrombin. GP Ib is present on platelet surfaces in a 1:1 ratio with GP IX.

Other membrane Glycoproteins : Membrane glycoproteins GPIa-IIa, GPIc – IIa, mediate platelet adhesion to collagen, fibronectin, laminin and vitronectin. GP V forms a noncovalent complex with GP Ib – IX in the platelet membrane. PECAM-1 binds to heparin like molecules. GPIV is a receptor for thrombospondin. GP IV is also reported to bind collagen.

Other Platelet Proteins : Other proteins presented in the platelet are platelet factor 4, β thromboglobulin, thrombospondin, platelet derived growth factor, fibronectin.

Platelet Factor 4: PF4 binds heparin with high affinity and neutralizes its anticoagulant activity. It exhibits a variety of activities, including the potentiation of platelet aggregation.

PLATELET BIOCHEMISTRY

The platelet has minimal ability to synthesize protein because it contains only low levels of RNA and lacks a nucleus. In terms of dry weight, the platelet is composed of approximately 60% protein, 15% lipid and 8% carbohydrate. Platelet minerals include magnesium, calcium potassium and zinc. Platelets contain substantial amounts of vitamin B12, folic acid, and ascorbic acid.

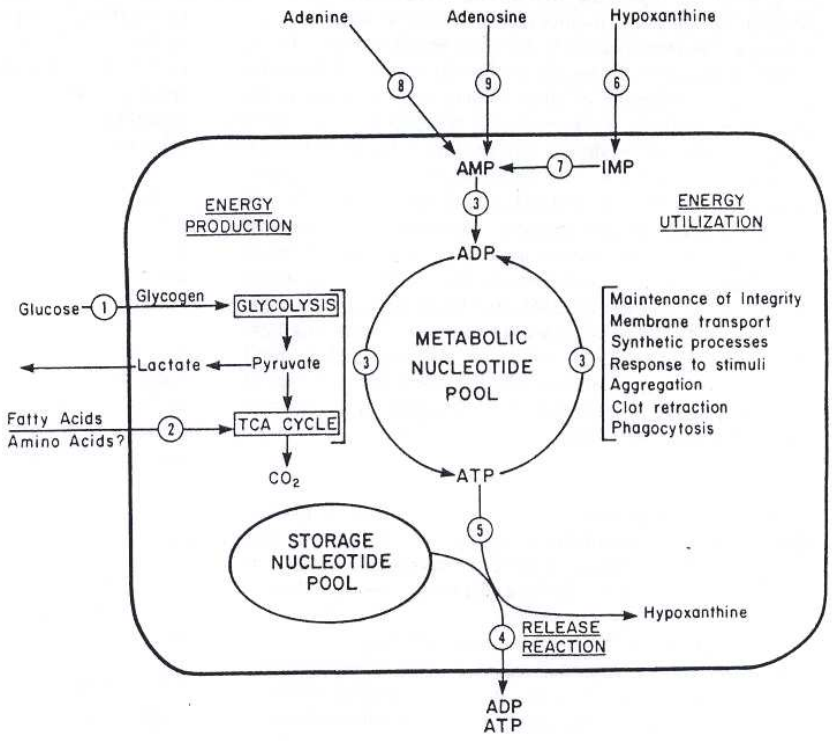
Platelet Energy Metabolism

There are several similarities between the energy metabolism of the platelet and that of skeletal muscle. Both involve active glycolysis and the synthesis and use of large amounts of glycogen and in both, the major mediator of intracellular energy use in an actomyosin-like adenosine triphosphatase. The platelet, like muscle, is metabolically adapted to expend large amounts of energy rapidly during aggregation, the release reaction, and clot retraction.

The major energy source for the platelet is glucose, which is rapidly taken up from the plasma.

A simplified scheme of platelet energy metabolism is shown in the figure below. Platelet energy is derived from the metabolism of glucose and to a lesser extent from the metabolism of fatty acids. Energy is provided in approximately equal amounts by glycolysis and the citric acid cycle. The

platelet energy reserve is provided by the metabolic pool of platelet nucleotides that is in a state of continuous turnover.



(Platelet energy metabolism)

Nucleotide Metabolism

Adenine nucleotides constitute 90% of free platelet nucleotides and are partitioned into at least two different pools, which undergo minimal interchange. The metabolic or cytoplasmic pool makes up 40% of total adenine nucleotides; it is used for the maintenance of various energy-consuming cell functions and is retained during platelet release.

The storage pool, which is present in the dense bodies, contains approximately two-thirds of the total platelet nucleotides, mainly in the form of

ADP and ATP. It is metabolically inactive, does not rapidly incorporate exogenous adenine or phosphate, and equilibrates slowly with the metabolic pool. Nucleotides in this pool are extruded from the platelet during the release reaction and cannot be replenished after release. ATP hydrolysis is required for conversion of G actin to F-actin. The ATP that is broken down to provide energy for the release reaction is not rephosphorylated, but rather is irreversibly degraded to hypoxanthine which diffuses out of the cell. Platelets also contain guanine nucleotides and uracil and cytosine pyrimidines.

Arachidonate Metabolism

Arachidonic acid is released from platelet membrane phospholipids after stimulation by numerous agonists through the enzymatic action of phospholipase A2 or the combination of phospholipase C and diglyceride lipase. After release, arachidonic acid can be acted on by either lipoxygenase, which results in the production of peroxy and hydroxy fatty acids, or by cyclooxygenase, which ultimately results in production of thromboxanes and prostaglandins.

Platelet "Coagulation" Factors

Numerous platelet proteins interact with plasma coagulation proteins although the mechanisms by which platelet membrane component become reorganized and capable of functioning as a catalytic surface for plasma proteins are not known.

Several plasma coagulation factors are associated with platelets, including von Willebrand factor, coagulation inhibitors, and factor XIII.

Various substances associated with or derived from the platelet have been designated platelet factors 1 to 10 and denoted by Arabic numerals. The most important of these are PF4 and PF3.

Platelet Factor 3

PF3 is required in at least two steps in the process of blood coagulation, namely the interaction between factors IXa and VIIIa, which results in the activation of factor X, as well as the interaction between factor Xa and factor Va which leads to the formation of prothrombinase. These coagulation reactions are greatly accelerated on the platelet surface.

PLATELET COUNT

The normal platelet count varies between

1,50,000 – 3,50,000 / mm^3

ORIGIN OF PLATELETS FROM MEGAKARYOCYTES

The megakaryocyte is a large hematopoeitic cell, the cytoplasm of which fragments to form circulating blood platelets. The histogenesis of platelets from megakaryocytes was first described by James Wright in 1910. The megakaryocytes are sessile polyploid cells which inturn descend from diploid

pluripotent hematopoeitic stem cells of marrow. The megakaryocytes are imprisoned within the sub endothelial layer of marrow sinuses by their very girth and volume (average 5000 femtolitres, Zhang YJ, 1991). In these marrow niches, mononuclear progenitors undergo diploid doublings by the unique process of endomitosis. Subsequently the polypoid megakaryocytes accumulate a bulky compartmentalized cytoplasmic mass with large volumes that at end stage maturation disintegrates abruptly to yield between 1000 and 8000 platelets having a volume of 7-9 femto litres each (Martin et al, 1982; Stenberg and Levin, 1989; Corash, 1989). Megakaryocytes are suicidal microorgans whose mission is to proliferate and then fragment their cytoplasm on demand to maintain blood platelets at relatively steady levels of about 1,50,000 – 3,50,000 / mm3.

Maintenance of platelet counts within this range represents a surplus of over 10 times that necessary to ensure routine haemostasis but provides a precautionary reserve for times of excess platelet loss or consumption.

PLATELET LIFE SPAN, TURN OVER & REMOVAL

Platelet life span, based on the time required to clear labeled platelets from circulation, has been estimated to be 8-12 days in humans. The sites for platelet removal appear to be the spleen, the liver & bone marrow. Degranulation and loss of density and platelet constituents has not been shown

to decrease platelet life span indicating that the number of haemostatic interactions may not be a key component.

PLATELET ADHESION, ACTIVATION & AGGREGATION

The anti thrombotic properties of intact vascular endothelium include potent platelet inhibitors. These inhibitors include PGI_2, NO & CO which are labile molecules that are released by endothelial cells and act locally as autocoids and ADPase, an ectonucleotidase of endothelial membranes that breaks down platelet activating ADP.

Adhesion

On vascular intimal injury, the antiplatelet properties of endothelium are diminished locally, while previously cryptic, thrombogenic subendothelial substances eg. collagen become exposed to flowing blood. Circulating platelets recognize sites of vascular disruption and undergo the process of adhesion to the site of injury. Platelet adhesion is mediated by von willebrand factor which is present in the extracellular matrix of sub endothelial vessel wall. The receptor of von willebrand factor on the platelet surface is localized in membrane glyco protein (Gp) Ib, part of the platelet membrane Gp Ib / IX-V complex. Platelet adhesion is also facilitated by direct binding to subendothelial collagen by means of specific platelet membrane collagen receptors.

Activation

Adherent platelets then become activated. The platelet activation process results from the combined actions of several agonists that bind to their respective membrane receptors on adherent platelets and transmit platelet activating intracellular signals. These platelet stimuli include humoral mediators in plasma (epinephrine, thrombin), mediator released from activated cells, (ADP serotonin), vessels wall extracellular matrix constituents that come in contact with adherent platelets (eg. collagen, von willebrand factor). Activated platelets then undergo release reaction during which they secrete prepackaged constituents of their cytoplasmic granules. The constituents released from dense granules are ADP, ATP serotonin. The constituents released from alpha granules are soluble adhesive proteins (fibrinogen, von willebrand factor, thrombospondin, fibronectin), growth factors (PDGF, TGF α, TGF β) procoagulants (platelet factor 4, Factor V). Simultaneously, activated platelets synthesize denovo and release the potent platelet activator and vasoconstrictor thromboxane A2 (TX A_2)

Aggregation

The products of the platelet release reaction, including secreted granule constituents and TXA_2 mediate aggregation. During platelet aggregation (platelet – platelet interaction), additional platelets are recruited from circulation to the site of vascular injury leading to the formation of an occlusive

platelet thrombus. At lower shear levels (eg. in venous circulation), the molecular glue that mediates aggregation is fibrinogen, which can be derived either from plasma or from the alpha granule releasate of activated platelets. At higher shear level (eg. in arteries) von willebrand factor can substitute for fibrinogen as the ligand of aggregation. Fibrinogen or von willebrand factor binds to the specific platelet membrane receptor that are located in the Gp IIb / IIIa integrin complex and mediates aggregation and finally the platelet plug is formed. The platelet plug is anchored and stabilized by the fibrin mesh that develops simultaneously as the product of the coagulation cascade.

PATHOGENESIS OF ACUTE MYOCARDIAL INFARCTION

Almost all myocardial infarction result from coronary atherosclerosis, generally with superimposed coronary thrombosis. During the natural evolution of atherosclerotic plaques, especially those that are lipid laden, an abrupt and catastrophic transition may occur characterized by plaque rupture. After plaque rupture there is exposure of substances that promote platelet activation and aggregation, thrombin generation and ultimately thrombus formation. The resultant thrombus that is formed interrupts blood flow and leads to an imbalance between oxygen supply and demand and if this imbalance is severe and persistent, to myocardial necrosis.

PLATELET VOLUME & CARDIOVASCULAR DISEASE

As the initial step in the pathogenesis of acute myocardial infarction is plaque erosion or rupture followed by platelet adhesion, activation & aggregation followed by thrombus formation, platelets with more activity will predispose to the occurrence of myocardial infarction. Mean platelet volume (MPV) correlates with platelet function and activation, whether measured as aggregation, thromboxane synthesis, β thromboglobulin release, procoagulant function or adhesion molecule expression. (Bath et al, 1996).

Increased platelet reactivity as well as shortened bleeding time are associated with increased platelet volume (Milner & Martin, 1985; Trowbridge & Martin, 1987). Large platelets are metabolically and enzymatically more active than small platelets as assessed by invitro aggregometry (Corash et al 1977) and they have a higher thrombotic potential (Karpatkin 1972). They also express higher levels of procoagulatory surface proteins such as P – selectin (Mathur et al, 2001) and glycoprotein III a (Pathansali et al, 2001).

Large platelets are denser, they produce more thromboxane A_2 per unit volume of platelet cytoplasm and decrease bleeding time more than control platelets. Larger platelets aggregate more rapidly upon collagen challenge, release more serotonin & other granule contents and express more receptors per unit area (Pizzuli et al, 1998).

Platelet morphology and physiology are determined during or even before fragmentation of their precursor cell, the megakaryocyte (Rabellino et al 1981). Although the mechanism is still unclear, megakaryocyte ploidy seems to correlate closely with platelet volume (Hoffman and Long 1995). Although ploidy and platelet volume are independent variables, alterations in both parameters usually occur in tandem (Trowbridge and Martin, 1987). Certain cytokines such as Interleukin-3, thrombopoetin and in particular interleukin 6 (IL-6) seem to have a major influence on megakaryocyte ploidy leading to the production of larger and more reactive platelets (Debilli et al 1993; Brown et al 1997). Recently a frequent G/C polymorphism in the promoter region of IL-6 at nucleotide position (-174) has been shown to influence IL-6 serum levels (Fishman et al 1998). In individuals carrying the common G allele, higher IL-6 levels have been found compared with the levels in carriers of the C allele (Fishman et al 1998)

Large platelets are not necessarily young platelets (Martin et al, 1983) and there is now no convincing evidence that platelets appreciably change volume or density as they circulate (Penington, 1976).

Various studies found an association between mean platelet volume and coronary artery disease or the occurrence of an acute myocardial infarction (Martin et al 1991; Pizzuli et al 1998) while others observed no effect (Halbmayer et al 1995)

Platelet volume and prognosis following acute myocardial infarction

Hendra et al (1988) observed that all patients with severe cardiac failure had larger platelet volumes than patients with mild or no failure. Osuna et al (1998) stated that increase in mean platelet volume on admission was an independent risk factor for cardiac failure.

Increased MPV was found to be an independent risk factor for recurrent myocardial infarction by Martin et al (1982).

Yilmaz et al (2004) observed that in patients with dilated cardiomyopathy and in sinus rhythm, an increased MPV was associated with an increased incidence of left ventricular thrombus.

In contrast to the above observations, Cameron et al (1983) noted that the increase in MPV did not appear to provide any prognostic information after myocardial infarction. The value in patients who died was no different from that of the survivors. The MPV did not correlate with the more established factors determining prognosis after myocardial infarction such as size of the infarct.

AGE, SEX AND MPV

Funiak et al (1994) observed increased MPV in patients of advanced age. In contrast Bancroft et al (2000) observed decreased MPV with advanced age. He observed no difference between genders.

MPV AND SMOKING

Smokers were found to have an increased MPV (Tschope et al, 1989; Kario et al, 1992).

MPV AND OTHER DISEASES

An increased MPV was observed in diabetics compared with non diabetics by Sharpe et al (1993).

Although Osuna et al (1998) observed a higher MPV in those with systemic hypertension, Bath et al (1996) observed no such effect.

Ford et al (1998) observed that patients with hyperthyroidism had increased MPV.

Bansal et al (2002) stated that MPV was increased in patients with chronic obstructive pulmonary disease and this could possibly contribute to an increased incidence of pulmonary embolism in these patients.

In chronic liver disease, MPV and platelet count are decreased (Jorgensen et al, 1984).

MPV AND DRUGS

Aspirin has no effect on MPV (Pizulli et al, 1998). Recently, invitro data on the therapeutic effects on platelet volume of losartan, an angiotensin II receptor antagonist or Doxasosin, an α 1 adrenoceptor antagonist, have been reported (Jagroop and Mikhailidis 2001). These observation have not been confirmed in vivo (Jagroop and Mikhailidis 2000).

AIMS AND OBJECTIVES

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1. To assess the mean platelet volume in patients with acute myocardial infarction and to compare the results with the control group.
2. To identify whether any association exists between mean platelet volume and other selected risk factors like age, sex, family history of coronary artery disease, smoking, systemic hypertension, diabetes mellitus.
3. To find out the role of mean platelet volume in short term outcome after acute myocardial infarction .

MATERIALS AND METHODS

MATERIALS AND METHODS

Setting : Dept of Medicine and Intensive Coronary Care Unit, Govt. Rajaji Hospital and Madurai Medical College, Madurai

Collaborating Department : Dept of Cardiology, Govt. Rajaji Hospital and Madurai Medical College , Madurai.

Design of Study : Observational prospective analytical study.

Period of Study : February 2005 - July 2005

Sample Size : 40 Patients and 20 controls

Ethical Committee approval : The present project was approved by the ethical committee.

Inclusion Criteria :

Patients who had a history suggestive of acute myocardial infarction and whose ECG showed ST segment elevation of >1mm in two contiguous limb leads or ≥ 1mm in two contiguous chest leads.

Exclusion Criteria :

1. Not having typical ECG changes.
2. Presence of septicemia.
3. Known cases of any hematological disorders.
4. Presence of blood loss

5. Presence of hyperthyroidism or other endocrine disorders.
6. Presence of chronic liver disease
7. Presence of chronic obstructive pulmonary disease
8. Presence of chronic renal failure on erythropoietin therapy.
9. Past history of cerebrovascular accident.
10. Known cases of any malignancies.

Controls :

Age and sex matched subjects who did not have angina pectoris, ECG evidence of coronary artery disease, history of previous coronary artery disease and who met the above exclusion criteria were kept as controls.

Consent :

Informed consent was obtained from all those who participated in the study or their relatives.

Materials :

Thus a total of 40 cases who satisfied the inclusion and exclusion criteria stated above were taken up for subsequent study. 20 age and sex matched subjects were kept as control.

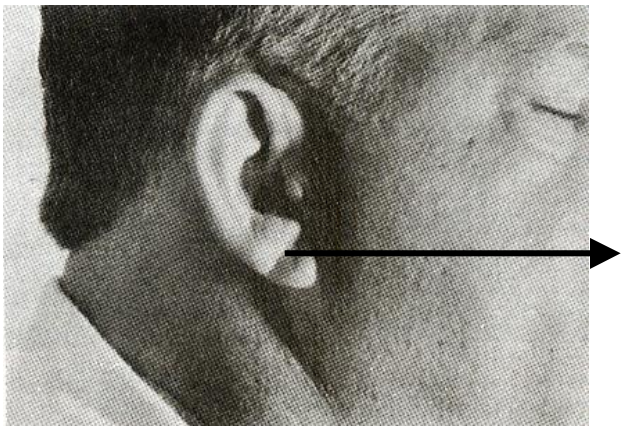
Definitions used for the study:

1. Acute Myocardial Infarction:

A patient was considered to have acute myocardial infarction if he / she gave a definite clinical history suggestive of acute myocardial infarction and had ECG changes suggestive of acute myocardial infarction as mentioned in the inclusion criteria above.

2. Diagonal earlobe crease:

A subject was considered to have diagonal earlobe crease if he/she had a crease running from anterior to posterior and from upward to downward direction in the lower part of the pinna as showed in the picture below.



3. Smoking :

A subject was considered to be a smoker if he / she gave a history of tobacco smoking within the past 20 years. Person who had quit smoking completely before 20 years were not considered as smokers.

4. Systemic hypertension ;

A subject was considered to have systemic hypertension if he was already diagnosed to have systemic hypertension and was on anti hypertensive medication or if the systolic blood pressure during the hospital stay was found to be more than or equal to 140 mm Hg and / or the diastolic blood pressure was more than or equal to 90 mm Hg according to the JNC VII report.

5. Diabetes Mellitus :

A subject was considered to have diabetes mellitus if he/she was already diagnosed to have diabetes mellitus or during the hospital stay was found to have a

- fasting plasma glucose of $\geq$ 126mg/dl

  Or

- 2 Hour postprandial plasma glucose $\geq$ 200mg/dl

  Or

- Symptoms of diabetes mellitus plus random blood sugar $\geq$ 200 mg /dl

6. Family history of coronary artery disease :

A subject was considered to have a family history of premature coronary artery disease if there was

- a history of coronary artery disease in male first degree relative < 55 years

  Or

- a history of coronary artery disease in female first degree relative < 65 years

7. Left ventricular dysfunction :

Left ventricular dysfunction was divided to mild, moderate, severe according to ejection fraction in ECHO

≤ 29%	Severe
30 - 39	Moderate
40 - 49	Mild

8. Short term outcome - outcome at the end of 7 days after acute myocardial infarction was considered with respect to left ventricular dysfunction, left ventricular clot in ECHO, recurrence of angina, occurrence of arrhythmia, occurrence of death.

Methods:

Selected socio-demographic, clinical and laboratory data were collected from the patients and controls and recorded in a proforma. (enclosed in Appendix – Appendix I)

I. Socio demographic data comprised of :

- Age
- Sex
- History of tobacco smoking
- Family history of coronary artery disease

II. Clinical data

- Diagonal earlobe crease
- Clinical examination.

III Laboratory Data

- Blood sugar
- ECG
- Echocardiogram
- Platelet count
- Mean Platelet volume

ECG – 12 lead multi channel ECG was taken in all the patients

ECHO – Transthoracic ECHO was done using ALOKO PRO S 100 in all the cases. 2-D ECHO, M- MODE ECHO was done to analyse the regional wall motion abnormality, presence of clot and also to assess the left ventricular function. Colour doppler evaluation was done to evaluate the presence of valvular regurgitation and also to assess the diastolic function.

For the above mentioned haematological parameters, 2 ml of blood was withdrawn by venepucture from the patients within 24 hrs of admission to the hospital. The venepucture site was properly cleaned and blood withdrawn and

collected in EDTA containing disposable tubes available in the market. The sample was transported immediately to a quality controlled centre where the sample was analysed for platelet volume. The instrument used for analysis was COBAS MICROS OT 18 automated haematological analyser made by ROCHE.

The instrument was started up. After start up, a pipette appeared from the instrument. Blood sample was fed to the instrument by the principal worker. The pipette drew the necessary amount of blood and withdrew on its own after taking the necessary amount of blood. From that moment a waiting time of 180 seconds appeared on the instrument. At the end of 180 seconds, a print out with the platelet count and mean platelet volume was ejected from the printer connected to the instrument.

The instrument was repeatedly standardized for quality control.

Conflict of interest :

There was no conflict of interest.

Financial support:

Nil

Limitations:

1. Technical constraints and cost factor of the investigation have led to limited number of cases.

2. Since the lipid levels were found to be independent of mean platelet volume in earlier studies, it was neither considered for the present study nor taken for analytical purposes.

Statistical Analysis :

Data were entered in Microsoft excel spread sheet and analysed utilizing the software-Epidemiological Information Package 2002 (Epi Info 2002) - developed by the centre for disease control and prevention, Atlanta for World Health Organisation. Range, Median, Mean and Standard deviation and ‘p’ values were calculated using this package. Chi-square test was done to find out the significance of relationships between the groups. Significance was considered if the ‘p’ value was below 0.05.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

The total number of subjects included in the study was 60. Among the 60 subjects, 40 were cases and 20 were controls and their profile is furnished below.

Age distribution

The age of the cases ranged from 35 to 75 years and that of controls ranged from 35 to 66 years. The mean and standard deviation for the cases were 55.4 ± 9.1 years and those for the controls were 53.5 ± 7.3 years. There was no significant difference with respect to age among them. The distribution of cases and controls with respect to age is given in the table -1 given below.

Table 1

Distribution of cases and controls with respect to age

Age Group	Case		Control	
	No.	%	No.	%
< 30	-	-	-	-
30-39	2	5	1	5
40-49	5	12.5	3	15
50-59	20	50	12	60
60 & above	13	32.5	4	20
Total	40	100	20	100
Range	35-75		35-66	
Median	55		52	
Mean	55.4		53.5	
S.D.	9.1		7.3	

'p'= 0.4002 (not significant)

Sex composition

Among the 40 cases studied, there were 32 males and 8 females. Among the controls, there were 15 males and 5 females. The difference in the sex composition of the case and control group was not statistically significant. The details are furnished in table - 2 depicted below.

Table 2

Distribution of cases and controls in relation to gender

Sex	Case		Control	
	No.	%	No.	%
Males	32	80	15	75
Females	8	20	5	25

'p'= 0.4476 (not significant)

Diagonal earlobe crease

Among the 40 cases, 21 had diagonal earlobe crease. Among the 20 controls, 4 had diagonal earlobe crease. The diagonal earlobe crease was significantly present among cases than controls. The details are given in the table-3 given below.

Table 3

Distribution of cases and controls with respect to the presence of diagonal earlobe crease

Diagonal earlobe crease	Case		Control	
	No.	%	No.	%
Yes	21	52.5	4	20
No	19	47.5	16	80

'p'= 0.0332 (significant.)

Family history of coronary artery disease

Among the 40 cases, 8 had a family history of coronary artery disease. Among the 20 controls, 4 had a family history of coronary artery disease. The difference in the percentage of subjects with a family history of coronary artery disease was not statistically significant. The details are shown in the table 4 given below.

Table 4

Distribution of cases and controls with respect to family history of coronary artery disease

Family History	Case		Control	
	No.	%	No.	%
Yes	8	20	4	20
No	32	80	16	80

'p'= 0.9999 (not significant)

Smoking

Among the 40 cases, 24 had the habit of smoking. Among the 20 controls, 7 had the habit of smoking. There were no female smokers in either group. There was no statistical difference in the habit of smoking between cases and controls. The details are depicted in the table-5 given below.

Table 5

Distribution of cases and controls with respect to the habit of smoking

Smoking	Case		Control	
	No.	%	No.	%
Yes	24	60	7	35
No	16	40	13	65

'p'= 0.1205 (not significant)

Systemic hypertension:

Among the 40 cases, 8 had systemic hypertension. Among the 20 controls, 5 had systemic hypertension. Systemic hypertension was present among cases and controls without any statistically significant difference. The details are provided in the table 6 given below.

Table – 6

Distribution of cases and controls with respect to the presence of systemic hypertension.

Systemic Hypertension	Case		Control	
	No.	%	No.	%
Yes	8	20	5	25
No	32	80	15	75

'p'= 0.4476 (not significant)

Diabetes Mellitus

Among the 40 cases, 11 had diabetes mellitus. Among the 20 controls, 6 had diabetes mellitus. There was no statistically significant difference among cases and controls with respect to diabetes mellitus. The details are given in the table – 7 shown below.

Table – 7

Distribution of cases and controls with respect to the presence of diabetes mellitus.

Diabetes Mellitus	Case		Control	
	No.	%	No.	%
Yes	11	27.5	6	30
No	29	72.5	14	70

'p'= 0.9193 (not significant)

History of previous Myocardial Infarction

Among the 40 cases, 8 had a history of previous myocardial infarction. The details are given in Table – 8 given below.

Table - 8

Distribution of cases with respect to the presence of history of previous myocardial infarction.

Previous MI	Case	
	No.	%
Yes	8	20
No	32	80

Aspirin intake

Among the 40 cases, 11 were taking aspirin. The details are given in the table – 9 given below.

Table – 9

Distribution of cases with respect to the presence of aspirin intake

On Aspirin	Case	
	No.	%
Yes	11	27.5
No	29	72.5

Platelet Count

The mean platelet count of the cases was 2.05 ± 0.46 lakhs/mm^3. The mean platelet count of the controls was 2.24 ± 0.39 lakhs / mm^3. There was no significant difference in the platelet count between the cases and controls. The details are given in table – 10 furnished below.

Platelet Count in Cases and Controls

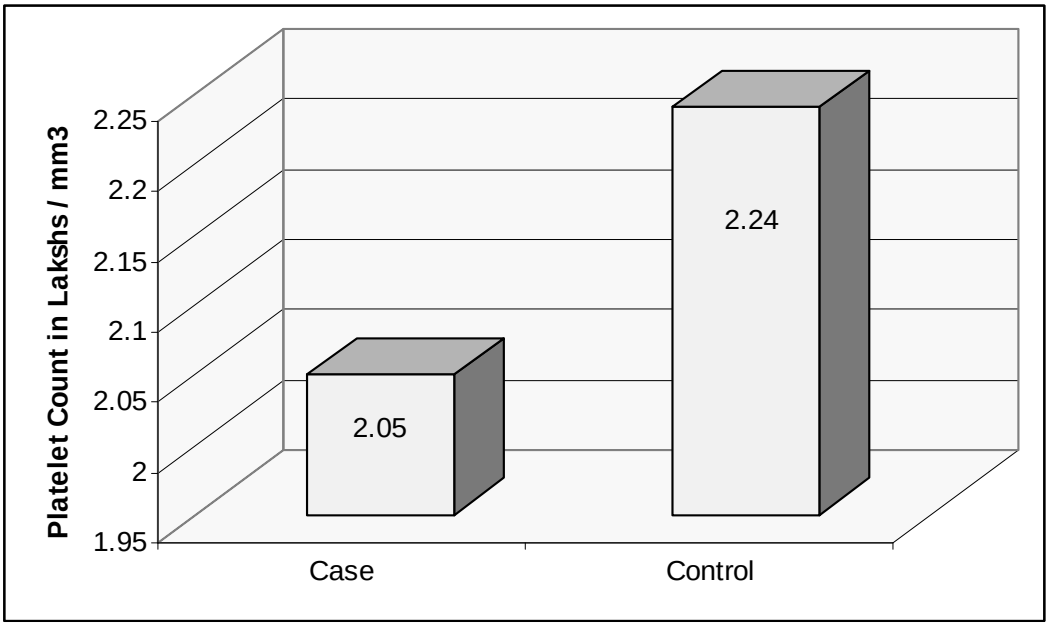


Table – 10

Platelet count in cases and controls

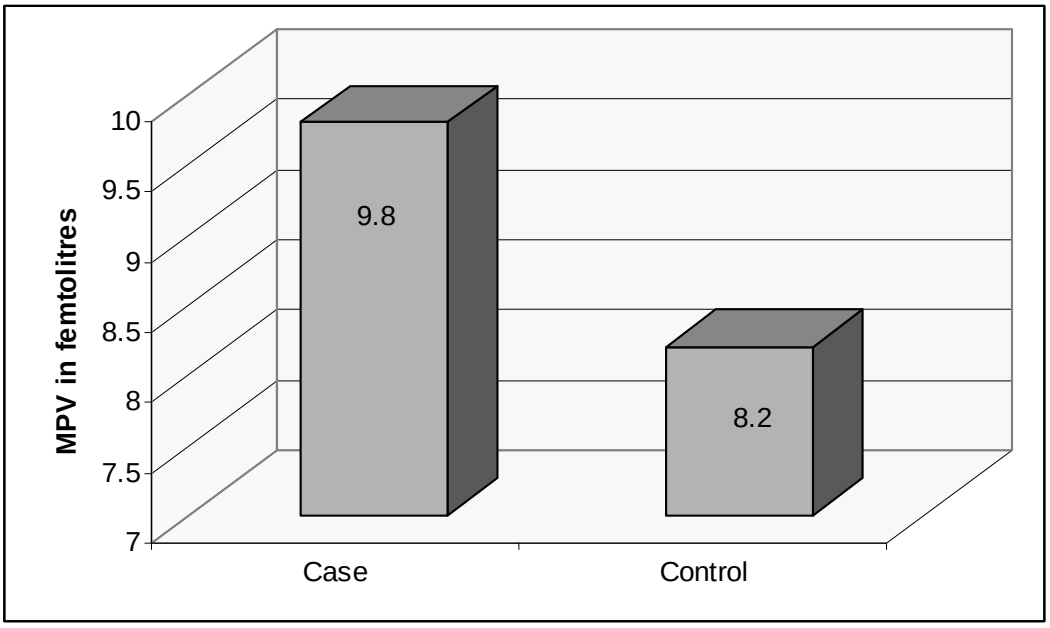
Platelet Count	Case		Control	
	No.	%	No.	%
Upto 1.5	5	12.5	-	-
1.5 – 2.49	30	75.0	16	80
2.5 – 3.49	5	12.5	4	20
3.5 & above	-	-	-	-
Total	40	100	20	100
Range	1.2 – 3.19		1.69-3.06	
Median	2.02		2.13	
Mean	2.05		2.24	
S.D.	0.46		0.39	

'p'= 0.1241(not significant)

Mean Platelet Volume

The mean platelet volume of the cases ranged from 8.8 to 10.8 femtolitres. The mean platelet volume of the controls ranged from 7.7 to 9.4 femtolitres. The mean ± S.D of the cases was 9.8 ± 0.56 femtolitres. The mean ± S.D of the controls was 8.2 ± 0.43 femtolitres. A comparative analysis of the mean platelet volumes between the cases and controls showed a statistically significant difference. The details are given in the table – 11 given below

MPV in Cases and Controls



Wall Distribution of Myocardial Infarction

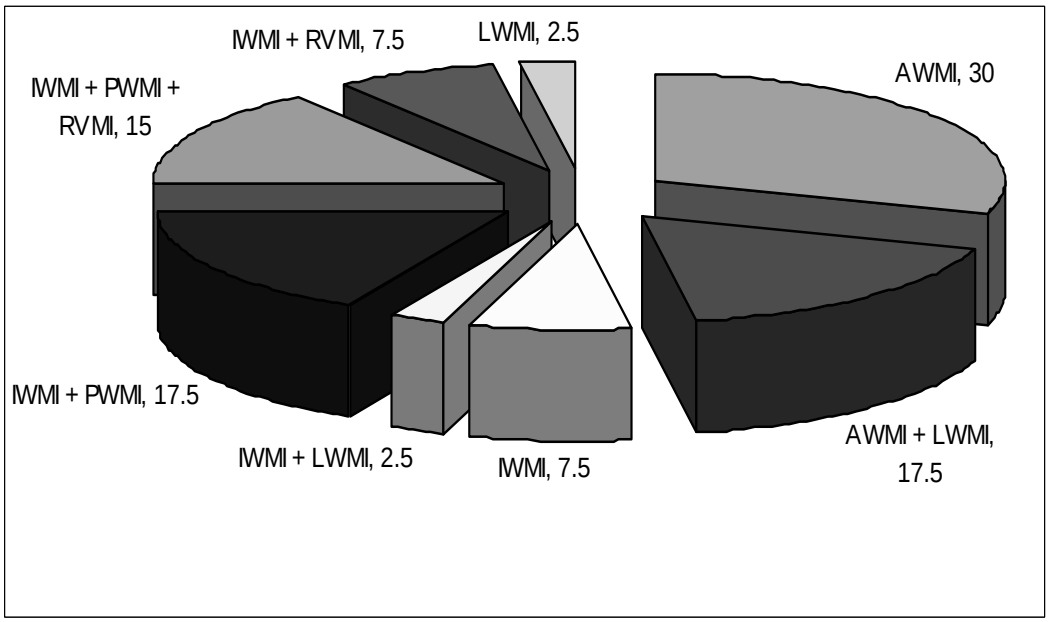


Table – 11

MPV in cases and controls

MPV	Case	Control
Range	8.8-10.8	7.7-9.4
Median	9.8	8.1
Mean	9.8	8.2
S.D.	0.56	0.43

'p'= 0.0001 (significant)

Wall Distribution of Myocardial Infarction

The wall distribution of myocardial infarction is shown in table – 12 given below.

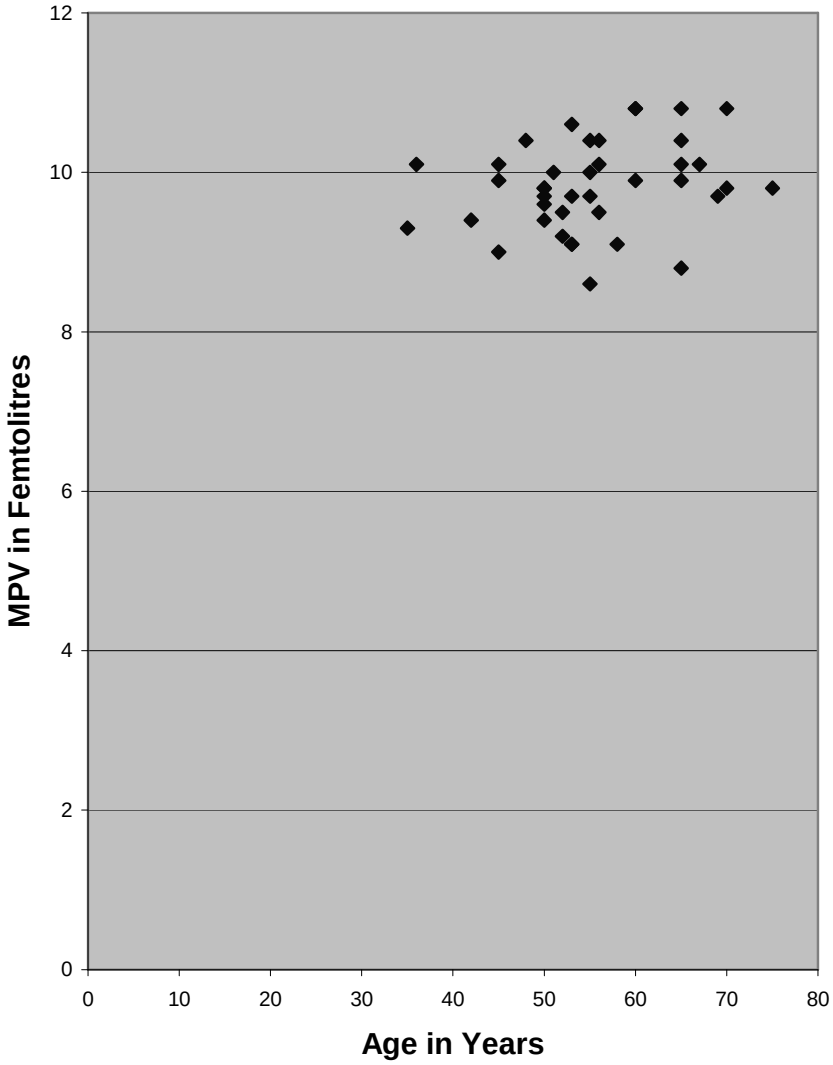
Table – 12

Wall Distribution of Myocardial Infarction

Wall Distribution	No.	%
AWMI	12	30
AWMI + LWMI	7	17.5
IWMI	3	7.5
IWMI + LWMI	1	2.5
IWMI + PWMI	7	17.5
IWMI + PWMI + RVMI	6	15
IWMI + RVMI	3	7.5
LWMI	1	2.5

Anterior Wall was found to be the most involved (30%).

Age and MPV in Cases



RELATIONSHIP BETWEEN MPV AND OTHER PARAMETERS

Table – 13

Relationship between Age & MPV

Age Group	MPV Values			
	Range	Median	Mean	S.D.
< 30	-	-	-	-
30-39	9.3 – 10.1	9.7	9.7	0.57
40-49	9 – 10.4	9.9	9.76	0.56
50-59	8.6 – 10.6	9.7	9.67	0.51
60 & above	8.8 – 10.8	10.1	10.13	0.59

'p' = 0.121 (not significant)

The relationship between age and MPV is not statistically significant.

Table – 14

Relationship between Sex & MPV

The mean MPV for males was 9.81 ± 0.56 femtolitres. The mean MPV for females was 9.9 ± 0.61 femtolitres. MPV was found to be independent of gender.

Sex	MPV Values			
	Range	Median	Mean	S.D.
Males (32)	8.6 – 10.8	9.85	9.81	0.56
Females (8)	9.1 – 10.8	9.75	9.9	0.61

'p' = 0.9729 (not significant)

Table – 15

Relationship between Diagonal earlobe crease and MPV

Diagonal earlobe crease	MPV Values			
	Range	Median	Mean	S.D.
Yes (21)	8.8 – 10.8	9.9	10.01	0.53
No (49)	8.6 – 10.8	9.6	9.63	0.55

'p' = 0.0376 (significant)

There exists a statistically significant relationship between diagonal earlobe crease and increased MPV values.

Table – 16

Relationship between family history of coronary artery disease and MPV

Family History	MPV Values			
	Range	Median	Mean	S.D.
Yes (8)	8.8 – 10.8	9.9	9.89	0.6
No (32)	8.6 – 10.8	9.8	9.82	0.56

'p' = 0.709 (not significant)

The relationship between family history of coronary artery disease and MPV was not significant.

Table – 17

Relationship between smoking and MPV

Smoking	MPV Values			
	Range	Median	Mean	S.D.
Yes (24)	8.8 – 10.8	9.95	9.87	0.49
No (16)	8.6- 10.8	9.75	9.77	0.67

'p' = 0.438 (not significant)

The mean MPV among smokers was 9.87± 0.49 femtolitres. The mean MPV among non smokers was 9.77 ± 0.67 femtolitres. Even though the mean MPV was higher among the smokers, it was not statistically significant.

Table – 18

Relationship between systemic hypertension & MPV

Systemic Hypertension	MPV Values			
	Range	Median	Mean	S.D.
Yes (8)	9.1 – 10.8	9.95	9.95	0.6
No (32)	8.6 – 10.8	9.8	9.8	0.56

'p' = 0.4658 (not significant)

There was no significant relationship between systemic hypertension and MPV.

Table – 19

Relationship between Diabetes Mellitus & MPV

Diabetes Mellitus	MPV Values			
	Range	Median	Mean	S.D.
Yes (11)	9 – 10.8	9.7	9.78	0.53
No (29)	8.6 – 10.8	9.9	9.85	0.58

'p' = 0.5948 (not significant)

The relationship between diabetes mellitus and MPV was not statistically significant.

History of previous Myocardial Infarction and MPV

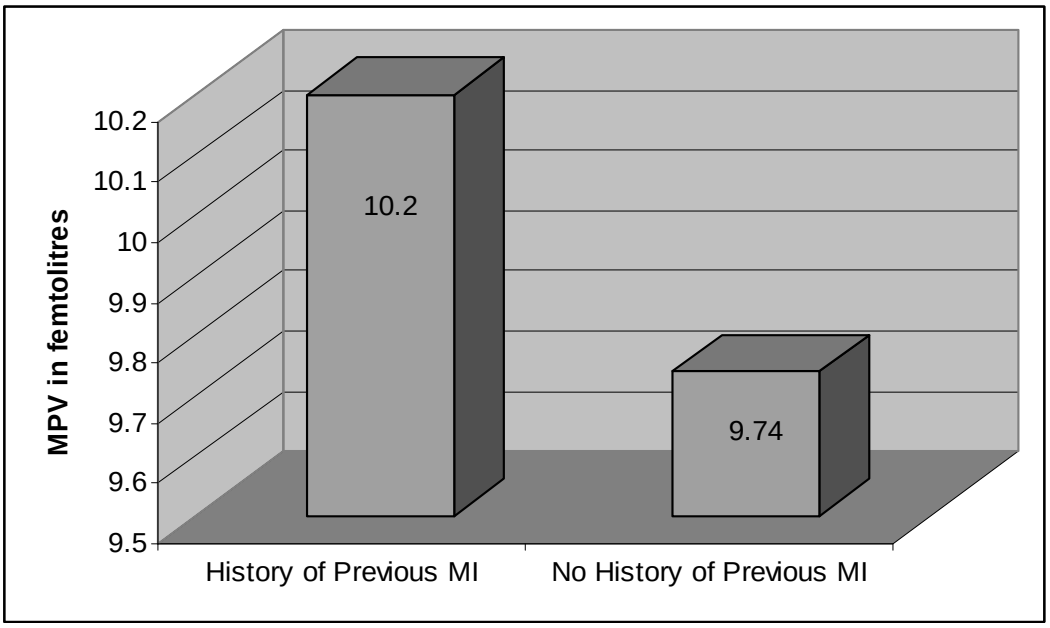


Table – 20

Relationship between history of previous myocardial infarction and MPV.

Previous MI	MPV Values			
	Range	Median	Mean	S.D.
Yes (8)	9.5 – 10.8	10.25	10.2	0.48
No (32)	8.6 – 10.8	9.75	9.74	0.55

'p' = 0.0435 (significant)

The mean MPV in cases with a previous history of myocardial infarction was 10.2±0.48 femtolitres. The mean MPV in cases without a previous history of myocardial infarction was 9.74±0.55 femtolitres. A significant difference was observed between the cases with previous myocardial infarction and those without previous myocardial infarction.

Table – 21

Relationship between Aspirin intake and MPV

On Aspirin	MPV Values			
	Range	Median	Mean	S.D.
Yes (11)	8.8 – 10.8	9.8	9.91	0.66
No (29)	8.6 – 10.8	9.8	9.8	0.53

'p' = 0.5739 (not significant)

The relationship between aspirin intake & MPV was not statistically significant.

Table – 22

Relationship between platelet count & MPV

Platelet Count (in lakhs / mm^3)	MPV Values			
	Range	Median	Mean	S.D.
Upto 1.5 (5)	9.2-10.4	9.9	9.88	0.44
1.5 – 2.49 (30)	8.6-10.8	9.8	9.86	0.6
2.5 – 3.49 (5)	9.1-10.1	9.4	9.58	0.44
3.5 & above	-	-	-	-

'p' = 0.5616 (not significant)

There was no significant relationship between platelet count and MPV.

Table – 23

Relationship between ejection fraction & MPV

Ejection Fraction	MPV Values			
	Range	Median	Mean	S.D.
$\leq$ 29 (2)	10.6-10.8	10.7	10.7	0.14
30-39 (3)	9.7-10.4	10.1	10.07	0.35
40-49 (22)	8.6-10.4	9.8	9.78	0.61
50 & above (13)	8.8-10.4	9.8	9.73	0.44

'p' = 0.1488 (not significant)

The mean MPV in cases with ejection fraction $\leq$ 29 was 10.7 $\pm$ 0.14 femtolitres. Although this value was higher than the other groups with higher ejection fractions it was not statistically significant.

Table – 24

Relationship between the presence of LV Clot & MPV

Clot	MPV Values			
	Range	**Median**	**Mean**	**S.D.**
Yes (2)	10.4-10.8	10.6	10.6	0.28
No (38)	8.6-10.8	9.8	9.8	0.55

'p' = 0.536 (not significant)

The mean MPV in cases with the presence of LV clot was observed to be higher than those without LV clot, but there was no statistical significance.

Table – 25

Relationship between recurrence of angina and MPV

Recurrence of angina	MPV Values			
	Range	**Median**	**Mean**	**S.D.**
Yes (2)	9.8-10.8	10.3	10.3	0.7
No (38)	8.6-10.8	9.8	9.8	0.55

'p' = 0.2898 (not significant)

Although the mean MPV in cases with recurrence of angina was higher than the rest, it was not statistically significant.

Table – 26

Relationship between survival without complications and MPV

Survival without complications	MPV Values			
	Range	Median	Mean	S.D.
Yes (18)	8.6-10.8	9.85	9.83	0.54
No (22)	8.8-10.8	9.8	9.83	0.59

'p' = 0.87 (not significant)

The relationship between survival without complications and MPV was not statistically significant.

Table – 27

Relationship between occurrence of death and MPV

Death	MPV Values			
	Range	Median	Mean	S.D.
Yes (4)	9-10.8	9.45	9.68	0.83
No (36)	8.6-10.8	9.85	9.85	0.54

'p' = 0.4692 (not significant)

The MPV of the patients who died was not statistically significantly different from those who survived.

DISCUSSION

DISCUSSION

Myocardial infarction is a major cause of morbidity and mortality in developed countries and is becoming a major problem in developing countries like India. Endogenous and exogenous risk factors like smoking, hypercholesterolemia, diabetes mellitus and systemic hypertension significantly increase the individual risk for myocardial infarction. However they only explain a part of the cases and there may be other relevant risk factors which need to be identified. Large platelets are more reactive, produce more thrombotic factors (Martin et al, 1983) and aggregate more easily (Haver et al, 1981).

Endler et al (2002) stated that mean platelet volume (MPV) is an independent risk factor for myocardial infarction. Similar observations were made by Martin et al (1983), Cameron et al (1983). But all these are studies conducted in the west with healthy western people serving as controls. So in this study an attempt was made to find out if any association existed between the platelet size and the occurrence of myocardial infarction among Indian population as reports are scanty.

In the study, the ages of the cases ranged from 35 to 75 years . The mean was 55.4 ± 9.1 years. The maximum number of cases i.e., 20 cases fell in the age group 50-59 years. This comes to 50% of the total cases. This pattern

corresponds to the pattern reported in India, which is as follows. Coronary artery disease appears a decade earlier compared with the age incidence in developed countries and the peak period is attained between 51-60 years. (Park K, 2005).

In the present study the relationship between age and MPV was not statistically significant where as Funiak et al (1994) found that MPV was significantly increased in patients of advanced age and it was statistically significant. But Bancroft et al (2000) stated that MPV decreases with age. But our study did not conform to any of the observations made by the above two workers.

Among the 40 cases, there were 32 males (80%) and 8 females (20%). Before menopause, women have a lower age adjusted incidence and mortality for coronary heart diseases than men. Gender specific incidence rates converge after menopause, suggesting a major role for estrogen in delaying progression of atherosclerosis. Much of this effect results from beneficial action of estrogen on lipid fractions. Estrogen reduces LDL - C by 10-15% while increasing HDL - C.

In the present study MPV was independent of genders. This is in parallel with the observation made by Bancroft et al (2000).

Among the 40 cases of myocardial infarction, 21 had the presence of diagonal earlobe crease (Frank’s sign), while only 4 among the 20 controls had

this. Lichstein et al (1976) stated that, ninety percent of patients over age 50 with significant triple vessel coronary disease had a deep ear lobe crease and that a unilateral ear crease was found to be associated with an intermediate degree of coronary obstruction. The ear lobe crease should be considered a strong and independent risk factor for coronary artery disease and NOT diagnostic for the presence of coronary artery disease, for which it is only 60% sensitive (Elliot et al, 1991).

Among the cases, those with diagonal earlobe crease were found to have a significantly higher MPV when compared to those without. Whether diagonal earlobe crease can be considered as an external marker for increased MPV needs to be further investigated.

8 cases among the 40 cases had a family history of coronary heart disease. Family history of premature coronary heart disease is a risk factor for coronary heart disease. Family history of premature coronary heart disease is considered positive if there is coronary heart disease in male first degree relative <55 years or if there is coronary heart disease in female first degree relative < 65 years.

In the present study no significant relationship was observed between a family history of coronary artery disease and MPV.

Among the 40 cases, 24 were smokers (60%) and among the 20 controls 7 were smokers (35%). Although this shows an increased prevalence of

smoking habit among those with coronary heart disease, it was not statistically significant. It has been calculated that in countries where smoking has been a wide spread habit, it is responsible for 25% of coronary heart disease deaths under 65 years of age (WHO 1979). A uniquely human habit, smoking has been identified as a major coronary risk factor. The small sample size may be the reason why a statistical significance was not observed between the cases and controls with respect to smoking.

Although the MPV was higher among smokers compared to controls, the relationship was not statistically significant. Tschope et al (1989) and Kario et al (1982) in separate studies found smokers to have an increased MPV. But Kishk et al (1985) observed no relation between smoking and MPV. Our finding runs in parallel with that of Kishk et al (1985).

Among the myocardial infarction patients 8 had systemic hypertension (20%). In a study conducted by Gupta et al (2001) on myocardial infarction, the prevalence of systemic hypertension in myocardial infarction patients was found to be 32.6%.

In the present study no statistical relationship was observed between systemic hypertension and MPV. Bath et al (1996) also observed the same in their study. In contrast, Osuna et al (1998) observed a higher MPV in those with systemic hypertension.

11 patients (27.5%) in the present study had diabetes mellitus. This is similar to the prevalence of diabetes mellitus in myocardial infarction patients in the study by Gupta et al (2001), which was 21%.

The MPV in patients with diabetes mellitus did not vary from those without diabetes mellitus. Sharpe et al (1993) stated that MPV was significantly increased in diabetic subjects compared with non diabetics. They stated that since the platelet size is a determinant of platelet function, with larger platelets being more reactive per unit volume, the platelets might play a part in the micro and macro vascular complications of diabetes mellitus. Osuna et al (1998) also observed a higher MPV with diabetes mellitus. The fact that in our study, no relationship was observed may be due to the small sample size.

Of the 40 patients studied, 8 had a previous attack of myocardial infarction.

The MPV in patients with a previous history of MI was significantly higher than those without a previous history of MI. Martin et al (1991) stated that increased MPV is an independent risk factor for recurrent MI. Osuna et al (1998) also stated that a large MPV was associated with a higher prevalence of prior MI. This finding of the present study runs in parallel with the observation made by the earlier workers.

In the present study 4 out of those with a previous history of myocardial infarction were on aspirin. 7 more patient were also on aspirin for angina. Thus

a total of 11 patients were taking aspirin. The MPV in patients on aspirin and in those not on aspirin was not statistically different Pizulli et al (1998) also stated that aspirin has no effect on platelet volume. However similar studies in larger population are required to confirm this observation.

The mean platelet count of the cases was 2.05± 0.46 lakhs / mm^3 and that of the controls was 2.24± 0.39 lakhs / mm^3. Although the mean platelet count among the cases was less compared to the controls it was not statistically significant. Senaran et al (2001) stated that patients with acute myocardial infarction had increased platelet counts. Their observation was that in patients with myocardial infarction, there was increased thrombopoeitin levels. Increased thrombopoeitin levels may increase both platelet counts and platelet size, resulting in haemostatically more active platelets, which may contribute to the development and progression of coronary artery disease. However the observation by Senaran et al (2001) was in contrast to that of Cameron et al (1983) as they noticed that patients with acute myocardial infarction had a reduced platelet count compared to the controls. They suggested that reduced platelet count may be due to the consumption of platelets at the thrombus site. But in our study, there was no significant difference in the platelet counts between the case and the control groups.

There was no significant relationship between platelet count and MPV in our study. There are contrasting views regarding this aspect. Senaran et al

(2001) observed both an increased platelet count and MPV in patients with myocardial infarction as stated above. But Camaron et al (1983) observed a reduced platelet count and higher MPV in patient with myocardial infarction. They stated that the reduced platelets count may be due to the consumption of platelets at the thrombus site as stated above. The observations in our study did not run in parallel with the findings of the above two workers.

The MPV of the cases ranged from 8.8 to 10.8 femtolitres with a mean of 9.8 ± 0.56 femtolitres. The MPV of the controls ranged from 7.7 to 9.4 femtolitres with a mean of 8.2±0.43 femtolitres. The difference between the two was statistically significant.

Previous studies on MPV and myocardial infarction have given different observations

Halbmayer et al (1995) stated that MPV did not differ significantly between patients and controls in their study. In contrast to this Cameron et al (1983) found an increased mean platelet volume among those with acute myocardial infarction compared to controls. Similar findings was observed by Martin et al (1983) in their study. Large platelets are denser, they produce more thromboxane A2 per unit volume of platelet cytoplasm. Larger platelets aggregate more rapidly upon collagen challenge, release more serotonin and other granule contents and express more receptors per unit area (Pizzuli et al,

1998). So an increased MPV, as an indicator of larger, more reactive platelets, may represent a risk factor for myocardial infarction (Endler et al, 2002).

One question is that, does the increase in platelet volume occur before the myocardial infarction or does it occur as a response to the platelet consumption in myocardial infarction. Martin et al (1983) who did a study on mean platelet volume in acute myocardial infarction measured platelet volume within 12 hours of admission to hospital and then later at 6 weeks. They stated that mean platelet volume was increased before myocardial infarction occurred for the following reasons. They said that the increase in volume seen within the first 12 hours of admission suggested that the increase was present before infarction, as the life span of the platelet is about 8 days. More than 90% of the platelet population whose distribution was measured after myocardial infarction were circulating before the vascular occlusion occurred. They also observed that the increase in MPV persisted six weeks after discharge from hospital, when the infarct would have been largely healed. This also supported the view that platelet volume was chronically larger in the infarct group.

Further proof that the increase in mean platelet volume occurs before acute myocardial infarction is got from the study conducted by Endler et al (2002). They evaluated mean platelet volume in patients presenting with acute myocardial infarction and in patients with a history of previous myocardial infarction which had occurred upto 37 years before the study. They compared it

with those without myocardial infarction. They found out that the MPV was significantly raised in those with acute MI and in those with a history of previous myocardial infarction when compared to those without myocardial infarction. They also observed that there was no significant difference in the MPV between those with acute myocardial infarction and those with a history of previous myocardial infarction. This showed that the time interval between the occurrence of MI and the estimation of MPV did not influence the value of MPV. This further adds to the proof that raised MPV precedes the occurrence of MI.

O'Malley et al (1995) conducted a similar study of MPV estimation in stroke patients. They estimated MPV in stroke patients within 48 hours of admission and also at 6 months later and compared it with controls. They found that MPV was significantly raised in stroke patients compared to controls. They suggested that the changes in MPV might have preceded the vascular event and is unlikely to be due to platelet consumption at the infarct site. They said that since the average life span of the platelets is about 8 days, the elevated MPV seen within the first 48 hours after stroke represented platelets released before infarction. Further more it was unlikely that platelet consumption due to the localized thrombosis would affect peripheral venous estimation of platelet variables. They further stated that since there was no difference in MPV between large cortical strokes and small lacunar infarcts, it was unlikely that

platelet consumption at the thrombus site would affect the peripheral venous estimation of platelet variables. They also added that, the fact that the observed increase in MPV had remained unchanged in post stroke survivors was further evidence that changes in MPV were likely to have preceded the acute event.

From these, we can assume that the increased MPV might have occurred before acute myocardial infarction and unlikely to have occurred after the event.

Although the highest MPV of 10.7 femtolitres was observed in those with the least ejection fraction i.e., $\leq$ 29%, there was no statistical significance. Hendra et al (1988) stated that all patients with severe cardiac failure had larger platelet volumes than patients with mild or no failure. Osuna et al (1998) also observed that an increased platelet volume was related to a higher risk of cardiac failure. But our study showed only non significantly higher platelet volumes in those with severe left ventricular dysfunction.

Although the mean MPV in cases with the presence of left ventricular clot was higher than those without left ventricular clot, it was not statistically significant. Yilmaz et al (2004) observed that in patients with dilated cardiomyopathy and in sinus rhythm, an increased MPV was associated with an increased incidence of left ventricular thrombus. But the number in one subgroup is too small to reach a logical conclusion.

The mean MPV in cases with recurrence of angina was 10.3 which was higher than the rest. But it was not statistically significant. Martin et al (1991) observed that the MPV was greater in those with a recurrent ischemic event. Osuna et al (1998) also observed that an increased MPV was associated with a non significant higher rates of ischemic events during the recovery phase of acute myocardial infarction. Here also the small number in one subgroup prevent us from reaching a logical conclusion.

There was no significant difference in MPV among the group that survived without complications and the rest. The 4 patients who died did not have a statistically significant higher MPV compared to the rest.

According to Cameron et al (1983), the increase in MPV did not appear to provide any prognostic information during the period of study. They observed that the values in patients who died was no different from that of the survivors. They observed that MPV did not correlate with more established factors determining prognosis after infarction such as the size of the infarct. Their observations were in contrast to the observations by Hendra J et al(1988), Osuna et al (1998) and Martin et al (1991) which have been cited above.

LIMITATIONS

1. The subgroup analysis could not be undertaken successfully as the number becomes small among sub groups. Hence statistically adequate

numbers should be included in future studies to arrive at valid conclusions.

2. Mathematical analysis by way of log probability studies among platelet volume and platelet count was not attempted.

AREAS OF FURTHER WORK

1. MPV studies in other thrombotic episodes.
2. Follow up study of MPV after the onset of clinical events and finding out the association between MPV and platelet count by apply the log probability formula.
3. Platelet volume studies among patients on losartan and doxasosin.
4. Invitro studies on factors contributing for thrombomegaly in order to introduce interventional measures.
5. Studies to find out the physiological mechanisms which regulate MPV within the megakaryocyte.

CONCLUSION

CONCLUSION

- MPV was significantly elevated in patients with acute myocardial infarction (9.8 ± 0.56 femtolitres) when compared with controls (8.2 ± 0.43 femtolitres).
- The presence of diagonal earlobe crease among cases was significant compared to controls.
- MPV in patients with acute myocardial infarction was found to be independent of age, sex, family history of coronary artery disease, smoking, systemic hypertension and diabetes mellitus.
- MPV was higher with the presence of diagonal earlobe crease among cases.
- A significantly higher MPV was noted in patients with a history of previous myocardial infarction.
- Aspirin was not found to have any significant association with MPV.
- There was no correlation between platelet count and MPV.
- No correlation was found between MPV and short term outcome after myocardial infarction.

SUMMARY

SUMMARY

The study 'Mean Platelet Volume in acute myocardial infarction' was done to assess the relationship between mean platelet volume (MPV) and the occurrence of acute myocardial infarction and to find out its association with the risk factors and short term prognosis after acute myocardial infarction.

With rigid criteria 40 patients were selected carefully and were evaluated on social, clinical and laboratory aspects after institutional ethical clearance with an informed consent. 20 subjects were taken as controls. The data were entered in Microsoft Excel spread sheet and analysed statistically.

There were 32 males and 8 females in the patient group. There were 15 males and 5 females in the control group. The mean age of the patient group was 55.4 ± 9.1 years and that of the control group was 53.5 ± 7.3 years (p value 0.4002 - not statistically significant). The diagonal earlobe crease was present in 21 patients and in 4 controls. The difference was statistically significant (p value 0.0332). The prevalence of family history of coronary artery disease, smoking, systemic hypertension, diabetes mellitus were noticed in both groups without statistical significance. The mean platelet count in cases was 2.05 ± 0.46 lakhs/mm^3 and that of the controls was 2.24 ± 0.39 lakhs/mm^3 (p = 0.1241 - not statistically significant). The MPV of the patients ranged from 8.8 to 10.8 femtolitres and that of the controls ranged from 7.7 to 9.4 femtolitres. The mean

± SD of the patients was 9.8 ± 0.56 femtolitres and that of the controls was 8.2 ± 0.43 femtolitres. This was statistically significant (p=0.0001). There was no significant relationship between age, sex, family history of coronary artery disease, smoking, systemic hypertension, diabetes mellitus, platelet count and MPV. MPV was higher among those with diagonal earlobe crease (p=0.0332-significant). The mean MPV in patients with a history of previous myocardial infarction was 10.20 ± 0.48 femtolitres and in those without a previous history of myocardial infarction was 9.74 ± 0.55 femtolitres which was statistically significant (p=0.0435). MPV was found to be independent of aspirin intake (p=0.5739-not significant). There was no correlation between MPV and short term prognosis like left ventricular dysfunction and death.

From the present study, it is concluded that MPV is significantly raised in patients with acute myocardial infarction compared to controls. MPV is independent of risk factors like age, sex, family history of coronary artery disease, smoking, systemic hypertension, diabetes mellitus. MPV is significantly higher in patients with a previous history of myocardial infarction. MPV does not correlate with short term outcome after acute myocardial infarction. Further research is required into the role of platelet volume in myocardial infarction pathology, outcome and most importantly, in individuals at risk of myocardial infarction. Whether MPV becomes a routinely requested test remains to be seen.

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APPENDIX I - PROFORMA

APPENDIX I

PROFORMA

MEAN PLATELET VOLUME IN ACUTE MYOCARDIAL INFARCTION

Case No :
Name :
Age :
Sex :
Occupation :
IP No :
DOA :
DOD :

Diagonal ear crease : Yes / No
Family History of CAD : Yes / No
Smoking : Yes / No
Systemic Hypertension : Yes / No If yes, under regular R_x? Yes / No
Diabetes mellitus : Yes / No If yes, under regular R_x? Yes / No

HISTORY

Chronic stable angina : Yes / No
Unstable angina : Yes / No
Previous MI : Yes / No
On aspirin : Yes / No
Time of onset of pain :
Time of admission :
Thrombolysed : Yes / No
Time of thrombolysis :

EXAMINATION :

Pulse :
BP :
S_3 :
Crackles < 50% of lung fields : Yes / No
Crackles > 50% of lung fields : Yes / No
Cardiogenic shock : Yes / No
Killip class : I II III IV

INVESTIGATIONS :

Blood sugar :
Urea :
Creatinine :
S.CPK :
S.CPK MB :
Platelet count :
Mean platelet volume :

ECG

ECHO

1. RWMA : Yes / No if yes, wall
2. Ejection fraction :
3. Diastolic dysfunction : Yes / No
4. Clot : Yes / No

OUTCOME

Survived without complications
Survived with complications
Cardiac failure
Recurrence of angina
Reinfarction
Arrhythmias

Death

APPENDIX II - MASTER CHART

APPENDIX II

MASTER CHART

CASES

Sl.No	GROUP	AGE	SEX	D.E.CREASE	FAMILY HIST.	SMOKING	SYS.H.T.	DIA.MELL.	PRE.M.I.	ON ASP.	PLAT.COUNT	MPV	AWMI	LWMI	IWMI	PWMI	RVMI	EJEC.FRA	CLOT	REC.OF ANGINA	ARRYTHMIA	SUR.WITH COMP.	DEATH
1	MI	45	1	1	2	2	2	2	2	2	1.45	9.9	1	2	2	2	2	43	2	2	2	2	2
2	MI	75	2	2	2	2	1	2	1	2	2.13	9.8	1	2	2	2	2	43	2	2	2	2	1
3	MI	53	1	1	2	1	2	2	2	2	1.92	10.6	1	2	2	2	2	28	2	2	2	2	2
4	MI	55	1	2	2	2	2	2	2	2	2.45	8.6	1	2	2	2	2	45	2	2	2	1	2
5	MI	42	1	2	2	1	2	2	2	2	2.14	9.4	1	2	2	2	2	50	2	2	2	1	2
6	MI	51	1	1	1	1	2	2	2	2	1.74	10	1	2	2	2	2	51	2	2	2	1	2
7	MI	56	1	1	1	1	1	2	1	1	2.14	10.4	1	2	2	2	2	44	2	2	2	1	2
8	MI	55	1	2	2	1	2	1	2	2	3.06	10	1	2	2	2	2	42	2	2	2	2	2
9	MI	67	1	1	2	1	2	2	2	2	2.08	10.1	2	2	1	2	2	34	2	2	1	2	2
10	MI	65	1	2	2	2	2	2	1	1	2	10.8	2	2	1	2	1	21	2	2	1	2	1
11	MI	52	1	2	1	2	2	1	2	2	1.67	9.5	1	1	2	2	2	42	2	2	2	2	2
12	MI	65	1	1	2	1	2	2	2	1	2.36	10.4	2	2	1	1	1	50	2	2	2	1	2
13	MI	60	1	2	2	1	2	2	2	2	1.69	9.9	2	2	1	1	1	60	2	2	1	2	2
14	MI	53	1	2	2	1	2	1	2	2	1.73	9.7	2	2	1	1	2	48	2	2	2	1	2
15	MI	53	2	2	2	2	1	2	2	2	2.27	9.1	2	2	1	2	1	46	2	2	1	2	1
16	MI	50	2	1	2	2	2	1	2	2	2.03	9.7	2	2	1	1	2	60	2	2	1	2	2
17	MI	65	1	1	1	1	2	2	2	1	1.81	8.8	1	2	2	2	2	50	2	2	2	2	2

Sl.No	GROUP	AGE	SEX	D.E.CREASE	FAMILY HIST.	SMOKING	SYS.H.T.	DIA.MELL.	PRE.M.I.	ON ASP.	PLAT.COUNT	MPV	AWMI	LWMI	IWMI	PWMI	RVMI	EJEC.FRA	CLOT	REC.OF ANGINA	ARRYTHMIA	SUR.WITH COMP.	DEATH
18	MI	52	1	1	2	1	1	2	2	2	1.2	9.2	1	1	2	2	2	60	2	2	2	2	2
19	MI	65	1	2	2	1	2	1	2	2	1.21	10.1	2	2	1	1	1	50	2	2	2	1	2
20	MI	58	1	2	2	1	2	2	2	2	2.24	9.1	2	2	1	1	1	48	2	2	2	2	2
21	MI	56	1	1	1	1	2	2	1	2	2.65	10.1	1	1	2	2	2	59	2	2	2	2	2
22	MI	69	1	1	2	1	2	2	2	1	1.7	9.7	1	1	2	2	2	42	2	2	2	2	2
23	MI	36	1	2	2	1	2	2	2	2	1.75	10.1	2	2	1	1	2	52	2	2	2	1	2
24	MI	65	2	1	2	2	2	2	2	2	2.32	9.9	2	2	1	2	1	48	2	2	2	1	2
25	MI	60	2	1	2	2	1	1	1	2	1.85	10.8	2	2	1	2	2	40	1	2	2	2	2
26	MI	50	1	1	2	1	1	2	1	1	2	9.8	2	1	2	2	2	46	2	1	2	2	2
27	MI	50	2	2	2	2	2	2	2	2	2.79	9.4	1	1	2	2	2	52	2	2	2	1	2
28	MI	55	1	2	2	1	1	2	1	2	1.33	10.4	2	2	1	1	2	36	1	2	2	1	2
29	MI	50	1	2	2	1	2	2	2	2	1.78	9.6	2	2	1	1	2	55	2	2	2	1	2
30	MI	45	1	2	2	2	2	1	2	1	2.43	9	1	1	2	2	2	48	2	2	2	2	1
31	MI	53	1	2	2	2	2	1	2	2	3.19	9.1	2	2	1	1	1	46	2	2	2	1	2
32	MI	50	1	1	2	2	2	1	2	1	1.8	9.8	1	1	2	2	2	52	2	2	2	1	2
33	MI	56	1	1	2	1	2	1	1	1	2.46	9.5	1	2	2	2	2	48	2	2	2	2	2
34	MI	35	1	2	2	1	2	2	2	2	2.74	9.3	1	2	2	2	2	43	2	2	2	1	2
35	MI	55	2	1	1	2	2	2	2	2	1.93	9.7	2	2	1	1	2	30	2	2	2	2	2
36	MI	48	1	1	2	2	2	1	2	2	2.2	10.4	1	2	2	2	2	42	2	2	2	2	2
37	MI	60	1	1	1	1	2	2	2	1	2.1	10.8	2	2	1	2	2	40	2	2	2	1	2
38	MI	70	1	1	1	1	2	2	2	2	1.38	9.8	2	2	1	1	2	46	2	2	2	1	2
39	MI	45	1	2	2	1	1	2	2	1	2.12	10.1	2	1	1	2	2	48	2	2	2	1	2
40	MI	70	2	1	2	2	2	2	2	2	2	10.8	2	2	1	1	1	40	2	1	2	2	2

Sex 1-Male, 2-Female Other Parameters 1-Yes, 2-No

CONTROLS

Sl.No	GROUP	AGE	SEX	D.E.CREASE	FAMILY HIST.	SMOKING	SYS.H.T.	DIA.MELL.	PLAT.COUNT	MPV
1.	CONTROL	50	1	2	2	1	2	2	2.14	8.3
2.	CONTROL	58	1	1	1	2	2	2	2.88	8
3.	CONTROL	35	1	2	2	1	2	2	2.45	9.4
4.	CONTROL	52	2	2	2	2	1	2	2	7.8
5.	CONTROL	48	1	2	1	2	2	2	1.8	8
6.	CONTROL	60	2	2	2	2	1	1	3.06	7.9
7.	CONTROL	56	1	2	2	1	2	2	2.62	8.9
8.	CONTROL	64	1	1	2	2	2	1	2.92	8.2
9.	CONTROL	50	2	2	2	2	1	2	1.8	7.7
10.	CONTROL	46	1	2	1	2	2	1	2	8.1
11.	CONTROL	58	1	2	2	1	2	2	1.69	8
12.	CONTROL	53	1	2	2	1	2	1	2.12	8.2
13.	CONTROL	66	1	2	2	2	1	2	2.41	8.5
14.	CONTROL	50	1	1	1	2	2	2	2	7.7
15.	CONTROL	48	2	2	2	2	2	2	1.88	8.3
16.	CONTROL	66	1	2	2	2	2	2	1.98	8.2
17.	CONTROL	55	1	2	2	1	1	1	2.4	8
18.	CONTROL	51	1	2	2	1	2	2	2.03	8.9
19.	CONTROL	52	1	1	2	2	2	2	2.4	7.9
20.	CONTROL	52	2	2	2	2	2	1	2.3	8.1

Sex	1-Male, 2-Female

Abbreviations in Master Chart

D.E.CREASE	Diagonal Earlobe Crease	LWMI	Lateral Wall Myocardial Infarction
FAMILY HIST.	Family History of coronary artery disease	IWMI	Inferior Wall Myocardial Infarction
SMOKING		PWMI	Posterior Wall Myocardial Infarction
SYS.H.T	Systemic Hypertension	RVMI	Right Ventricular Myocardial Infarction
DIA.MELL.	Diabetes Mellitus	EJEC.FRA	Ejection Fraction
PRE.M.I	Previous Myocardial Infarction	CLOT	
ON.ASP.	On Aspirin	REC OF ANGINA	Recurrence of Angina
PLAT.COUNT	Platelet Count	SUR.WITH.COMP	Survived with Complication
MPV	Mean Platelet Volume	ARRHYTHMIA	
AWMI	Anterior Wall Myocardial Infarction	DEATH	

For these Parameters 1-Yes, 2-No.

APPENDIX III
ABBREVIATIONS AND ACRONYMS

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ABBREVIATIONS AND ACRONYMS

ADP	- Adenosine diphosphate
AWMI	- Anterior Wall Myocardial Infarction
BP	- Blood Pressure
CAD	- Coronary Artery Disease
IWMI	- Inferior Wall Myocardial Infarction
LWMI	- Lateral Wall Myocardial Infarction
MI	- Myocardial Infarction
MPV	- Mean Platelet Volume
NO	- Nitric Oxide
PGI_2	- Prostacyclin
PWMI	- Posterior Wall Myocardial Infarction
RVMI	- Right Ventricular Myocardial Infarction
vWF	-Von Willebrand factor.